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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,705	04/17/2001	Yuki Abe	01149/HG	7090
1933	7590	01/16/2004	EXAMINER	
FRISHAUF, HOLTZ, GOODMAN & CHICK, PC 767 THIRD AVENUE 25TH FLOOR NEW YORK, NY 10017-2023				KERR, KATHLEEN M
		ART UNIT		PAPER NUMBER
		1652		

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/836,705	ABE ET AL.
	Examiner Kathleen M Kerr	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 08 October 2003.

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-60 is/are pending in the application.

4a) Of the above claim(s) 1-39, 44 and 46-55 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 40-43, 45 and 56-60 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) The translation of the foreign language provisional application has been received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6/10/03. 6) Other: NCBI Taxonomy browser excerpt.

DETAILED ACTION

Application Status

1. In response to the previous Office action, a non-Final rejection (mailed on May 29, 2003), Applicants filed an amendment and response received on October 8, 2003. Said amendment amended Claims 40-43 and 45 and added new Claims 56-60. Thus, Claims 1-60 are pending in the instant Office action.

Election

2. Applicants' petition of the restriction requirement, filed on October 8, 2003, which restriction was made final in the previous Office action, is noted. Said petition is still under consideration.

Claims 1-60 are pending in the instant application. Claims 1-39, 44, and 46-55 are withdrawn from consideration as non-elected inventions. Claims 40-43, 45, and 56-60 will be examined herein.

Priority

3. As previously noted, the instant application is granted the benefit of priority for the foreign application 2000-116591 filed in Japan on April 18, 2000 and 2000-117458 filed in Japan on April 19, 2000 as requested in the declaration. Receipt was previously acknowledged of papers submitted under 35 U.S.C. § 119(a)-(d), which papers have been placed of record in the file. Said papers are not in English; no English translations have been filed.

Information Disclosure Statement

4. The information disclosure statement originally filed on October 25, 2001 and refiled on June 10, 2003 has been considered. Two documents, Matsuoka *et al.* and Shiao *et al.* could not be considered due to the poor copies filed; new copies of these documents are required for their consideration.

As previously noted, the information disclosure statement filed on February 12, 2002 (Paper No. 12) has been reviewed.

Withdrawn - Objections to the Specification

5. Previous objection to the specification because the title is not descriptive is withdrawn by virtue of Applicants' amendment to the title.

Maintained - Objections to the Specification

6. Previous objection to the Abstract for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)) is maintained. Applicants have submitted a new Abstract but have failed to insert the changes suggested by the Examiner for completeness. The amended Abstract remains incomplete. As previously noted, "the Examiner suggests the inclusion of the source of the genes disclosed, *Penicillium citrinum*, as well as the names of the genes: *mlcE*, an efflux pump, and *mlcR*, and transcription factor, in the gene cluster disclosed." Correction is required.

Withdrawn - Claim Objections

7. Previous objection to Claims 40-43 and 45 for depending from non-elected Claims 29, 27, 26, and 1 is withdrawn by virtue of Applicants' amendments.

8. Previous objection to Claims 40-43 and 45 for containing non-elected subject matter is withdrawn by virtue of Applicants' amendments.

Withdrawn - Claim Rejections - 35 U.S.C. § 112

9. Previous rejection of Claims 40, 42-43 and 45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "encoding a modified amino acid" is withdrawn by virtue of Applicant's amendment.

10. Previous rejection of Claims 40, 42-43 and 45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "capable of accelerating the biosynthesis of ML-236B" is withdrawn by virtue of Applicants' amendment.

11. Previous rejection of Claims 40-43 and 45 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "vector...obtained from... *E. coli* FERM BP-70006" is withdrawn by virtue of Applicants' amendment; moreover, the new language in Claims 56 and 58 is clear.

12. Previous rejection of Claim 42 under 35 U.S.C. § 112, second paragraph, as being indefinite for the phrase "wherein the vector comprises no additional genes" is withdrawn by virtue of Applicants' amendment.

13. Previous rejection of Claim 43 under 35 U.S.C. § 112, second paragraph, as being indefinite for the distinction between recombinant mlcA protein and non-recombinant mlcA protein is withdrawn by virtue of Applicants' amendment.

14. Previous rejection of Claims 40, 42, 43, and 45 under 35 U.S.C. § 112, first paragraph, written description, is withdrawn by virtue of Applicants' amendment to include *structure* and function for the claimed variants.

15. Previous rejection of Claims 40-43 and 45 under 35 U.S.C. § 112, first paragraph, enabling deposit, is withdrawn by virtue of Applicants' amendment to the claims to remove reference to said deposit. New claims 56-58, which refer to the deposit, have this rejection set forth anew below.

Maintained - Claim Rejections - 35 U.S.C. § 112

16. Previous rejection of Claims 40-43 and 45 under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using host cells that contain the biosynthetic pathway for ML-236B (for example, *P. citrinum*), does not reasonably provide enablement for methods using host cells that do not contain the biosynthetic pathway for ML-236B is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the declaration under 35 U.S.C. § 1.132 by Inventor Abe obviates the rejection; the Examiner disagrees. The declaration states that *Penicillium citrinum*, *P. chrysogenum*, *P. notatum*, and *P. italicum* as well as *Eupenicillium sphaericum* can be used in the claimed methods. The Examiner does not disagree. However, these are but a few species of the numerous cells that can be used as "host cells" for the claimed invention, the breadth of which has not been enabled by the specification. Three *Penicillium* species (see attachment wherein *notatum* is a synonym for *chrysogenum*) and a single *Eupenicillium* species not identified by

NCBI (but found in the ATCC catalog, see attachment) are described in the declaration. These limited species do not enable use of all host cells, or even a reasonable number of kinds of host cells to produce ML-236B, an HMG-COA reductase inhibitor. The instant claims include making ML-236B in *E. coli*, yeast, even human cell lines, none of which are enabled by the specification which teaches the up-regulation of a polyketide synthase system natively found in the host cells meant to be used in the invention.

As previously noted, “the only working examples with *mlcR* involve its transformation into *P. citrinum*. While ML-236B production was not measured in these experiments, transcription of ML-236B biosynthetic genes was increased; thus it follows that ML-236B would be produced in such cells, likely at a higher rate. However, no examples of *mlcR*, or any ML-236B biosynthetic proteins, functioning outside its native *P. citrinum* are described in the instant specification or the art. The ability to recreate this polyketide production system in host cells other than *P. citrinum* is wholly unpredictable as evidenced in the polyketide synthase (PKS) field which requires numerous accessory proteins as well as a supply of appropriate precursors not usually found in non-polyketide producing cells to function in, for example, *E. coli* host cells. No guidance has been offered in the instant specification to meet this end. Thus, the instant claims are not enabled to the full extent of their scope.” For all of the above reasons, the instant rejection is maintained.

Withdrawn - Claim Rejections - 35 U.S.C. § 102

17. Previous rejection of Claims 42-43 under 35 U.S.C. § 102(a) as being anticipated by WO 01/12814 is withdrawn by virtue of Applicant’s amendment clarifying the language so as not to

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include particular members of the gene cluster taught by WO 01/12814. Since WO 01/12814 does not identify functions of genes on the cluster and does not expressly suggest exclusion of some and not others, exclusion of particular genes from the cluster prior to transformation for ML-236B production is neither taught nor indicated.

Maintained - Claim Rejections - 35 U.S.C. § 102

18. Previous rejection of Claims 40 and 45 under 35 U.S.C. § 102(a) as being anticipated by WO 2001/12814 is maintained. Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Applicants argue that the difference between the genomic DNA of WO 01/12814 and the cDNA taught by the instant application is significant to the invention; the Examiner disagrees. The genomic DNA taught by WO 01/12814 meets the structural limitations of 80% identity and at least one alteration of a polynucleotide encoding SEQ ID NO:42 and meets the functional limitation of the encoded protein since expression will disregard the introns. Applicants also argue that one of ordinary skill in the art would not have determined the cDNA sequence from the genomic sequence taught by WO 01/12814; the exclusion of Claim 41 in the instant rejection demonstrates that the Examiner agrees with this point.

NEW ISSUES

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 56-58 are rejected under 35 U.S.C. § 112, first paragraph, enabling deposit, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. To practice the instant methods, one of skill in the art is required to use FERM BP-7006 which is disclosed as containing pSAKexpR. While the instant specification contains limited deposit information, the requirements to enable such a deposit have not been fully met by the instant application. To enable the instant claims by enabling the deposit of DSM 12968, the following items are required: (1) the accession number assigned by the depository, (2) the date of deposit, (3) a brief description of the deposit, (4) **the name and full address of the depository** (37 C.F.R. § 1.801 - 1.809) (those which are in bold have not been fulfilled by the instant specification), and (5) the record must also contain a statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent (see M.P.E.P. § 2404.01); this statement may be certified by Applicants or Applicants' representative.

As previously noted, reference to the deposit is found in the specification on pages 10 and 31; said reference is incomplete by virtue of the missing full address. The specification must be amended to correct this defect. By virtue of Applicants' declaration of deposit filed, the record now contains a statement certifying that all restrictions on accessibility to said deposit be irrevocably removed by Applicant upon the granting of the patent. Only amendment to the specification is required.

20. Claims 56-60 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for methods using host cells that contain the

biosynthetic pathway for ML-236B (for example, *P. citrinum*), does not reasonably provide enablement for methods using host cells that do not contain the biosynthetic pathway for ML-236B. The instant rejection is set forth against the pending claims for the reasons of record for Claims 40-43 and 45, maintained above.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

21. Claim 60 is rejected under 35 U.S.C. § 102(a) as being anticipated by WO 01/12814.

The instant claim is drawn to methods of producing ML-236B in a host cell that has been transformed with a polynucleotide encoding SEQ ID NO:42.

WO 01/12814 teaches a 34203 base pairs gene cluster that, when transformed into *P. citrinum*, produces ML-236B. Said gene cluster contains the genomic DNA that encodes SEQ ID NO:42 (see Applicants' remarks filed October 8, 2003 and the English translation provided by Applicants of WO 01/12814). The "closed" language used in Claim 60 does not remove use of the entire cluster from the scope of the claimed method. Not only can other proteins be produced, but also the difference between genomic and cDNA is irrelevant (i.e., the insertions in the DNA sequence taught by WO 01/12814) upon protein expression since the same proteins will be produced by genomic or cDNA vectors.

Summary of Pending Issues

22. The following is a summary of the issues pending in the instant application:

- a) Complete copies of Matsuoka *et al.* and Shiao *et al.* references must be supplied to be considered.
- b) The Abstract stands objected to for not completely describing the disclosed subject matter.
- c) Claims 40-43, 45, and 56-60 stand rejected under 35 U.S.C. § 112, first paragraph, scope of enablement.
- d) Claims 56-58 stand rejected under 35 U.S.C. § 112, first paragraph, enabling deposit.
- e) Claims 40, 45, and 60 stand rejected under 35 U.S.C. § 102(a) as being anticipated by WO 01/12814.

Conclusion

23. Claims 40-43, 45, and 56-60 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

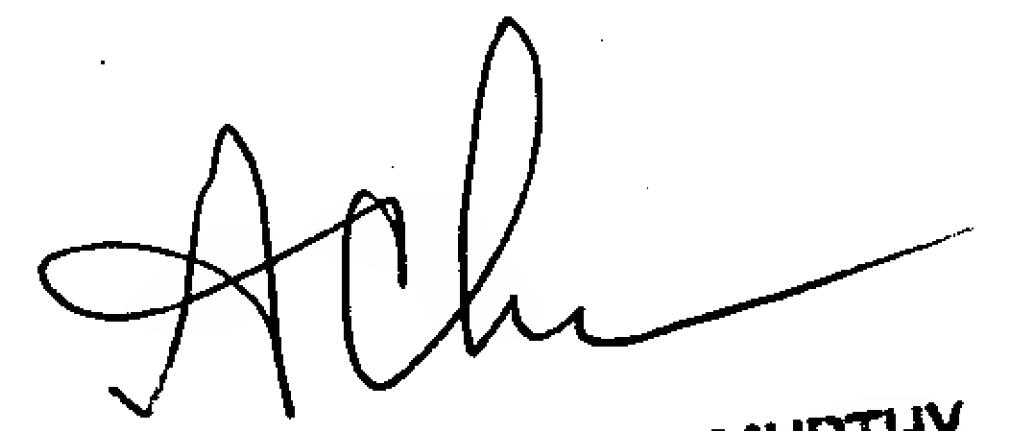
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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229.

The examiner can normally be reached on Monday through Friday, from 9:00am to 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



PONNATHUPURA CHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600



Kathleen M Kerr
Examiner
Art Unit 1652

January 7, 2004